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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR		ATTORNEY DOCKET NO.
09/491,146	01/25/00	KHUDYAKOV	Y	03063-0381

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EXAMINER	
BRUMBACK, B	
ART UNIT	**PAPER NUMBER**
1642	7

DATE MAILED: 09/10/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/491,146	Applicant(s) KHUDYAKOV ET AL.	
	Examiner Brenda G. Brumback	Art Unit 1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE ____ MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *14-19* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *14-19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *5* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Claims 13-19 are pending and examined on the merits.

Priority

2. An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the specification (37 CFR 1.78).

Information Disclosure Statement

3. The Information Disclosure Statement filed 01/25/2000 (Paper # 5) has been considered. A signed copy is attached hereto.

Claim Rejections - 35 USC § 112

4. Claims 13-19 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 13 is vague and indefinite in the recitation of "homologous antigenic peptides". The disclosure fails to teach the metes and bounds of "homologous" or "homologous peptides". While the specification teaches that the mosaic protein of the claimed invention comprises peptides corresponding from the same domains from different genotypes or subtypes

(see page 7, lines 4-10), it is unclear what degree of homology is required in order to determine that peptides of differing sequences belong to different genotypes or subtypes of a species. The specification fails to teach the parameters of how "homology" is to be determined and how much homology must be demonstrated in order to determine whether different viruses belong to the same or to different genotypes or subtypes of a species. Therefore, the metes and bounds of the invention as claimed cannot be determined.

5. Claims 13 and 14 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a "written description" rejection.

Vas-Cath Inc. V. Mahurka, 19 USPQ2d 1111, states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention, for purposes of the "written description" inquiry, is *whatever is now claimed*" (see page 1117). A review of the language of the claim indicates that these claims are drawn to a genus, i.e., mosaic proteins comprising a plurality of homologous antigenic peptides from different genotypes of an unspecified species or from different genotypes of a hepatitis virus. A description of a genus may be achieved by means of a recitation of a representative number of species falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial

portion of the genus. Regents of the University of California v. Eli Lilly & Co., 119 F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). In *The reagents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412), the court held that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. The court indicated that, while applicants are not required to disclose every species encompassed by a genus, the description of the genus is achieved by the recitation of a representative number of species falling within the scope of the claimed genus. At section B(1), the court states "An adequate written description of a DNA ... requires a precise definition, such as by structure, formula, chemical name, or physical properties, not a mere wish or plan for obtaining the claimed chemical invention".

There is a single species of the claimed genus disclosed that is within the scope of the claimed genus, *i.e.,* a nucleic acid encoding a mosaic protein comprising a plurality of antigenic peptides from different genotypes of hepatitis C virus (HCV). The disclosure of a single disclosed species may provide an adequate written description of a genus when the species disclosed is representative of the genus. However, the present claim encompasses numerous species other than the mosaic protein of HCV that are not further described. There is substantial variability among the species of the genus; the term "species", as is used in claim 13, encompasses all living organisms. The diversity among species of living organisms is well documented.

Weighing all factors, one skilled in the art would not recognize from the disclosure that the applicant was in possession of the genus of nucleic acids encoding mosaic proteins comprising antigenic peptides from different genotypes of any living organism. The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed" (see *Vas-Cath* at page 1116).

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. 112 is severable from its enablement provision (see page 1115).

6. Claims 13 and 14 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for nucleic acids encoding mosaic proteins comprising antigenic peptides from different genotypes of HCV, does not reasonably provide enablement for any nucleic acid encoding any mosaic protein comprising antigenic peptides from different genotypes of any living organism. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

The first paragraph of 35 U.S.C. 112 states, "The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same...". The courts have interpreted this to mean that the specification must enable one skilled in the art to make and use

the invention without undue experimentation. The courts have further interpreted undue experimentation as requiring "ingenuity beyond that to be expected of one of ordinary skill in the art" (Fields v. Conover, 170 USPQ 276 (CCPA 1971)) or requiring an extended period of experimentation in the absence of sufficient direction or guidance (In re Colianni, 195 USPQ 150 (CCPA 1977)). Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in In re Colianni, 195 USPQ 150, 153 (CCPA 1977) and have been clarified by the Board of Patent Appeals and Interferences in Ex parte Forman, 230 USPQ 546 (BPAI 1986). Among the factors are the nature of the invention, the state of the prior art, the predictability or lack thereof in the art, the amount of direction or guidance present, the presence or absence of working examples, the breadth of the claims, and the quantity of experimentation needed.

The instant disclosure fails to meet the enablement requirement for the full scope of the claims for the following reasons:

The nature of the invention: The claimed invention is drawn to a nucleic acid encoding a mosaic protein comprising a plurality of homologous antigenic peptides from different genotypes of an unspecified species or from different genotypes of a hepatitis virus.

The state of the prior art and the predictability or lack thereof in the art: The art teaches that the genotype of an organism constitutes the sum total of the genetic information contained in that organism (see "genotype", Academic Press Dictionary of Science and Technology, attached hereto). The art teaches multiple known genotypes of HCV (see Bhattacherjee et al., Journal of

General Virology 76:1737-1748, July 1995, page 1737, abstract and first paragraph) and multiple genetically distinct strains of hepatitis E virus (HEV) (see Khudyakov, Journal of Virology, 68/11:7067-7074, Nov. 1994; of record in Paper # 5), but does not teach multiple genotypes for other organisms.

The amount of direction or guidance present and the presence or absence of working examples: The specification discloses multiple genotypes of HCV and a nucleic acid encoding a mosaic protein comprising peptides from different genotypes of HCV. There is no disclosure of multiple genotypes of any other species of organism or from any other type of hepatitis virus. There are working examples drawn to construction of a nucleic acid encoding a mosaic protein comprising peptides from different HCV genotypes and diagnostic application of the mosaic protein; however, there are no working examples drawn to construction or application of a nucleic acid encoding a mosaic protein from different genotypes of any other organisms.

The breadth of the claims and the quantity of experimentation needed: Because the claims encompass nucleic acids encoding mosaic proteins comprising homologous antigenic peptides from different genotypes of any species of living organism or from different genotypes of any of the hepatitis viruses and because the art neither teaches multiple genotypes for organisms other than HCV and HEV nor teaches construction of nucleic acids encoding mosaic proteins of homologous antigenic peptides from organisms other than HCV and HEV, it would require undue experimentation by one of skill in the art to be able to make and use the invention commensurate in scope with the claims.

Claim Rejections - 35 USC § 102

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

a. Claims 13 and 14 are rejected under 35 U.S.C. 102(b) as being anticipated by Khudyakov et al. ("Artificial mosaic protein containing antigenic epitopes of hepatitis E virus, Journal of Virology, 68:7067-7074, Nov. 1994, of record in Paper # 5). Khudyakov et al. teach a synthetic gene encoding a mosaic protein comprising antigenic peptides of the Burmese and Mexican strains of hepatitis E virus (HEV) (see the abstract).

b. Claims 13 and 14 are rejected under 35 U.S.C. 102(b) as being anticipated by Fields et al. (Clinical and Diagnostic Virology 5:167-179, 1996; of record in Paper # 5). Fields et al. teach a synthetic gene encoding an artificial mosaic protein comprising antigenic peptides of the Burmese and Mexican strains of HEV (see the abstract, "Study design").

c. Claims 13-16 are rejected under 35 U.S.C. 102(a) as being anticipated by Ruedinger et al (Abstracts of the 97th General Meeting of the American Society for Microbiology, May 4-8 1997, abstract # V-54; of record in Paper # 5). Ruedinger et al. teach a synthetic gene encoding a mosaic protein comprising antigenic peptides of the core proteins of 11 different hepatitis C virus (HCV) genotypes.

d. Claims 13 and 14 are rejected under 35 U.S.C. 102(e) as being anticipated by Fields et al. (U.S. Patent 5,563,032; of record in Paper # 5). Fields et al. teach a nucleic acid encoding a mosaic protein comprising antigenically active regions from the Burma HEV strain and the Mexico HEV strain (see the abstract).

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 13-16 and 18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Khudyakov et al. (Journal of Virology), in view of Zhang et al. (Journal of Medical Virology 45:50-55, 1995; of record in Paper # 5), Bukh, et al. (Proc. Natl. Acad. Sci., U.S.A. 91:8239-

8243, 1994; of record in Paper # 5), and Chien et al. (Proc. Natl. Acad. Sci., U.S.A. 89: 10011-10015, 1992; of record in Paper # 5).

As set forth *supra,* Khudyakov et al. teach a synthetic gene encoding a mosaic protein comprising antigenic peptides of the Burmese and Mexican strains of HEV. Khudyakov et al. teach that mosaic proteins comprising more than one immunoreactive epitope are diagnostically useful because they imitate the immunologic function of the natural antigens without regard to other functions associated with the antigens, thus eliminating epitopes that may contribute to nonspecific reactivity. Khudyakov et al. teach that mosaic proteins for diagnosis of viral disease offer the additional advantage of having the ability to combine antigenic epitopes from different viral strains, thus increasing the sensitivity of the reagent and enhancing its usefulness for detection of varied strains of the target virus worldwide. Finally, Khudyakov et al. teach the successful preparation and immunodiagnostic application of mosaic proteins for diagnosis hepatitis E and B infections (see the abstract on page 7067 and the discussion on pages 7072-7073)

Zhang et al. teach that several different strains of HCV have been identified which can be divided into at least five distinct types. Zhang et al. describe synthesis of a panel of 16 type-specific peptides corresponding to variable antigenic regions within the HCV core, nonstructural 4 (NS4), and NS5 proteins and teach use of the peptides in an enzyme immunoassay for the detection of antibodies directed against five different HCV genotypes. Zhang et al. teach the locations of the corresponding HCV core and NS protein epitopes and list references for

obtaining the complete HCV nucleotide sequences (see the abstract and introduction on pages 50-51).

Bukh et al. teach the complete sequences of the core gene of 52 different HCV isolates that represent all 12 known genotypes of HCV (see the abstract).

Chien et al. teach a fused chimeric polyprotein comprising immunodominant epitopes of the nucleocapsid protein (c) and nonstructural proteins NS3-NS5 of HCV, and teach recombinant expression of the polyprotein (see pages 10011-10015, *Abstract, Introduction,* and *Materials and Methods*).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have made a synthetic gene for recombinant expression of a mosaic protein comprising immunodominant epitopes of the HCV core and/or NS proteins based on the sequence information provided by Zhang et al. and Bukh et al., according to the methods described by Chien et al. One of ordinary skill in the art at the time the invention was made would have been motivated to express the mosaic protein for use as an immunoassay reagent to detect HCV genotypes other than genotype 1a or 1b with greater sensitivity, as is suggested by Khudyakov et al.

Conclusion

9. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Bhattacherjee et al. (Journal of General Virology, 76:1737-1748, July 1995) teach six major genotypes of HCV and teach peptides corresponding NS4 peptides of the different genotypes (see page 1737, the abstract and Introduction).

Maggi et al. (Journal of Clinical Microbiology, 33/1:209-211, January 1995) teach marked diversity in the NS4 region of different genotypes (see especially the paragraph bridging pages 210-211).

Nagayama et al. (J. Clin. Invest., 92:1529-1533, September 1993) teach that the sensitivity of ELISA tests is influenced by heterogeneity in NS3 and NS4 sequences of different genotypes (see page 1529, abstract, and pages 1530-1532, Discussion).

10. Claims 17 and 19 are free of the prior art.

11. Amendment of claims 17 and 19 to be written in independent form, including all of the limitations of the base claims and any intervening claims would place these claims in condition for allowance.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brenda Brumback whose telephone number is (703) 306-3220. If the examiner can not be reached, inquiries can be directed to Supervisory Patent Examiner Anthony Caputa whose telephone number is (703) 308-3995. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Examiner Brenda Brumback, Art Unit 1642

and should be marked "OFFICIAL" for entry into prosecution history or "DRAFT" for consideration by the examiner without entry. The Art Unit 1642 FAX telephone number is (703)-305-3014. FAX machines will be available to receive transmissions 24 hours a day. In compliance with 1096 OG 30, the filing date accorded to each OFFICIAL fax transmission will be determined by the FAX machine's stamped date found on the last page of the transmission, unless that date is a Saturday, Sunday or Federal Holiday with the District of Columbia, in which case the OFFICIAL date of receipt will be the next business day.

BB
September 6, 2001

Brenda Brumback,
Patent Examiner